

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁴ : A61K 35/20, 37/02, C07K 3/24 C07K 15/00 // A61K 7/48	A1	(11) International Publication Number: WO 86/ 00525 (43) International Publication Date: 30 January 1986 (30.01.86)
(21) International Application Number: PCT/HU85/00042 (22) International Filing Date: 12 July 1985 (12.07.85) (31) Priority Application Number: 2751/84 (32) Priority Date: 13 July 1984 (13.07.84) (33) Priority Country: HU (71) Applicant (for all designated States except US): ECON- OMIX KÖZGAZDÁSZ EGYETEMI KISSZÖVET- KEZET [HU/HU]; Dimitrov tér 8, H-1093 Budapest (HU). (72) Inventor; and (75) Inventor/Applicant (for US only) : SZABÓ, Szigfrid [HU/HU]; Szivárvány u. 1. I/8, H-2040 Budaörs (HU). (74) Agent: PATENTBUREAU DANUBIA; P.O. Box 198, H-1368 Budapest (HU).		(81) Designated States: AT (European patent), AU, BE (Eu- ropean patent), BG, BR, CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, RO, SE (European patent), SU, US. Published <i>With international search report.</i>
(54) Title: PROCESS FOR THE PREPARATION OF A PHARMACEUTICAL COMPOSITION INFLUENCING THE TISSUE METABOLISM AND HAVING A REGENERATING ACTION (57) Abstract Preparation of a pharmaceutical composition influencing the tissue metabolism and having a regenerating action, which comprises adding crystal water-free potassium aluminium sulphate to a milk kept at a temperature above 90°C, then separating the solid material from the solution after the segregation of the obtained dispersion and optionally adding an aromatizing, perserving or colouring agent to the solution. The composition of the invention has an excellent regenerating action on the skin, muscle and bones. The metabolism disturbances of the tissues are also abolished, whereby the improve- ment of e.g. vascular stenoses can be achieved.		

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PROCESS FOR THE PREPARATION OF A PHARMACEUTICAL COMPOSITION
INFLUENCING THE TISSUE METABOLISM AND HAVING A REGENERATING
ACTION

5

Technical field

The invention relates to a process for the preparation of a pharmaceutical composition influencing the tissue metabolism and having a regenerating action, the effect of which mainly appears in promoting the tissue regeneration and assuring the tissue metabolism; however, this composition is also useful, inter alia for abolishing spastic muscle states and for relieving pain.

It has unexpectedly been recognized that a composition having the effects mentioned above can be obtained by adding crystal water-free potassium aluminium sulphate to a milk kept at a temperature above 90 °C, then separating the solution from the solid material after the segregation of the obtained dispersion and optionally adding aromatizing, preserving and colouring agents to the solution.

Disclosure of the invention

Based on these facts, the invention relates to the preparation of a pharmaceutical composition influencing the tissue metabolism and having a regenerating action. The process of invention comprises adding crystal water-free potassium aluminium sulphate to a milk kept at a temperature above 90 °C, separating the solution from the solid material after the segregation of the dispersion thus obtained and optionally adding aromatizing, preserving and colouring agents to the solution.

It can be supposed that the active agent of the composition prepared by using the process of invention is the whey obtained in the way described above. Although no mode of action is postulated, it is supposed that for the



tissue metabolism the products, the appropriate concentration of which is indispensable for the tissue regeneration in a given period, are provided by the amino acid content of the whey.

5 It has been proved by investigating the acid-base balance and the gas tension parameters as well as the changes in the whole resting respiratory function of the human body that the composition is rapidly and significantly absorbed through the skin. The acid-base balance is
10 shifted to a moderately metabolic acidosis which is then later shifted back to a mild alkalosis as a consequence of the amino acid metabolism.

 In addition to the general action mentioned above, the function of the respiratory system also becomes more
15 economical and the capacity thereof is enhanced by the composition of the invention.

 All these observations indicate that by using the composition of the invention metabolizing acidic substances, which are indispensable for a tissue regeneration, can be
20 advantageously introduced into the organism through the skin, that is, in a fully new way. These acidic substances exert an advantageous influence on the interior homeostasis of the cells and of the intercellular substance through the acid-base balance. The substances required for the tissue
25 regeneration are directly provided to the cells by the amino acid content of the composition of invention through a direct diffusion, i.e. without the intervention of the systemic blood circulation. As the application through the skin of such substances is unknown to our best knowledge,
30 a comparison to known oral or parenteral compositions is void of any sense.

 As starting materials of the process of invention, fatty cow milk can preferably be used, however a less fatty cow milk or e.g. goat's milk can also be used.

35 For treating the milk, crystal water-free potassium

aluminium sulphate, suitably alum heated at a temperature between 300 °C and 400 °C is used.

According to a practical embodiment of the process of invention, 1.6 to 2.1 g, depending from the fat content of the milk, of crystal water-free potassium aluminium sulphate are suitably added portionwise to 1 litre of milk, preferably at the boiling point of the milk, whereby the casein and fatty materials are precipitated. After some time, the supernatant becomes substantially pure and can be separated. For this purpose filtration and/or centrifugation are suitably used.

On carrying out the process of invention with a crystal water-free potassium aluminium sulphate obtained by heating natural or amorphous alum at 250 °C to melting and then up to the re-solidification /a spongy structure being formed/, after the segregation of the dispersion a completely pure solution is obtained, whereby a filtration becomes unnecessary.

The thus-obtained solution is actually suitable for a therapeutical use, but an aromatizing agent should be added for masking the inconvenient odour of the materials arising from the milk and a preserving agent has to be mixed in for preventing the decomposition of the materials arising from the milk. A colouring agent may also be added optionally to the composition for promoting the acceptability of the use thereof.

According to a preferred embodiment of the process of invention, an extract arising from a medicinal plant /herb/ is used as an aromatizing agent, whereby the inconvenient odours are fully masked and simultaneously, the medicinal plant extract may have an own advantageous action. The aqueous extract of woundwort /Solidago gigantea Ait. or Solidago serotina/, of Glechoma hederacea L., and of herb-ovy /Teucrium chamaedrys L./, or of silver-weed /Potentilla anserina L./ together with the above-mentioned

three medicinal plants may suitably be used as aromatizing agent. The aqueous extract can be prepared in a manner known in the art, suitably by boiling a mixture containing an 1:1 ratio by weight of the medicinal plants with water for 5 minutes and queezing the juice obtained through a press.

Instead of the medicinal plant extracts mentioned above, any other aromatizing agent commonly used in the pharmaceutical industry, such as pine, hay or orange aroma, may be used as aromatizing agent.

Similarly, preservatives commonly used for preparing pharmaceutical compositions may be used as preserving agents in the process of the invention. It is suitable to use ethanol, preferably pure ethanol of 96 %. Within a large-scale production, e.g. 70 % by volume of whey, 23 % by volume of pure 96 % ethanol and 7 % by volume of a medicinal plant extract /optionally containing 96 % ethanol, suitably 1 litre of pure 96 % ethanol for each 4 litres of the aqueous extract/, calculated for 1 litre of the pharmaceutical composition, may be used. Instead of ethanol, other preservatives may also be employed, by the use of which the whey liable to fermentation is preserved, the amino acid contents are not damaged, the treated skin is not irritated and the preserving effect is exerted even if the composition of the invention comes into contact with the skin.

Industrial applicability

The compositions prepared by using the process of the invention are utilized for pharmaceutical purposes as follows.

Suitable ready-for-use formulations of the compositions of the invention are the liniment, lotion and spray which may be prepared in a manner well-known in the pharmaceutical industry, optionally by employing the

additives commonly used for these types of pharmaceutical formulations.

Obviously, the amount and manner of the active substances used for a therapeutic purpose are dependent
5 on a number of factors such as the status of the patient, the effectivity and concentration of the active substance as well as the formulation.

The composition of the invention is suitably applied by infriction to the body part to be treated daily 2 to 5
10 times.

An optimum effect on diseases caused by vascular stenoses is provided by three treatments per day.

The treatment is carried out as follows.

The composition of the invention is applied to the
15 surface to be treated by hand or in a spray form. After absorption, the treatment is repeated and, after the second absorption, a third infriction is made. It is essential to keep the surface to be treated wet for about 10 minutes. As mentioned above, this treatment can be
20 accomplished daily 3 times.

In the course of a rehabilitation after knee operations, the use of lotions is convenient. In this case, it is suitable to pour the agent daily 5 to 10 times onto the body part covered with a compress.

25 The main therapeutic effects of the compositions prepared according to the process of the invention are as follows.

1. On the basis of the mode of action described above, it can be stated that the cellular activity is
30 stimulated and normalized by the amino acids introduced by the composition into the tissues, as the substances required thereto are provided in the appropriate quantity, time and manner.

2. A therapeutic chain reaction in several directions
35 is started in the organism as a consequence of the

regenerated advantageous cellular activity, whereby a rapid improvement or recovery is achieved in the following cases:

5 a/ A regenerating action on the skin, muscle and bones: the restoration of ulcers, gangrenes and other wounds, as well as a rapid rehabilitation after muscle lesions, cartilage- and syndesmoplastic operations and the like;

10 b/ Abolishment of metabolic disturbances: a restoring effect in vascular stenoses is achieved by the improvement of the metabolic economy in the musculature of the extremities, i.e. the metabolic disturbances thereof are abolished, while the blood circulation remains unchanged and the deficient states get a balance /in the cases of
15 arteriosclerosis obliterans, endarteriitis obliterans and the consequences thereof/;

c/ The composition of the invention shows an outstanding analgesic effect: the pain is abolished or alleviated to a minimum at 10 to 15 minutes after the
20 infriktion.

Modes of carrying out the invention

The invention is illustrated by the following non-limiting Examples.

25

Example 1

Commercially available crystalline alum /potassium aluminium sulphate; $KAl(SO_4)_2 \cdot 12H_2O$ is heated at a temperature between 300 °C and 400 °C, whereby the alum
30 becomes free from the crystal water, then it melts and re-solidifies. A spongy-structured material is obtained.

Fatty milk is heated to the boiling point and 1.8 g of the above-described spongy alum, calculated for 1 litre of milk, are added under continuous boiling. The mixture
35 is then boiled for 10 minutes and after the complete

precipitation of casein, the supernatant solid materials are removed from the milk surface by using a filter bag to give an opalescent, transparent liquid. After cooling down of the filtrate to a temperature between 35 °C and 40 °C, 1 litre of 96 % ethanol, calculated for each 4 litres of the filtrate, is added.

A decoction is prepared from 250 g of woundwort, 250 g of Glechoma hederacea L. and 250 g of herb-ovy with 6 litres of water during 5 minutes, whereupon the juice of the medicinal plants are queezed through a press to give a decoction of about 4 litres. Each 4 litres of this decoction is mixed with 1 litre of 96% ethanol.

75 ml of the decoction containing ethanol are added to 925 ml of the filtrate prepared as described above.

Example 2

The process described in Example 1 is followed, except that 200 g of woundwort, 200 g of Glechoma hederacea L., 200 g of herb-ovy and 200 g of silver-weed are used as medicinal plants.

The results of the pharmacological study on the compositions prepared according to the process of invention are described in the following Test Examples.

Test Example 1

The action of the composition prepared as described in Example 1 was investigated on 60 patients suffering from vascular stenosis /arteriosclerosis obliterans or endarteriitis obliterans/. Simultaneously, a control group consisting of 25 patients was treated by a traditional method commonly used in the medicinal practice and a control group consisting of 25 patients was treated with a liquid having the same colour and odour as that of the agent but containing no whey /negative control/. The agent was applied daily

3 times to the affected body parts by infriction as described above. No improvement was stated on the negative control group; a little improvement was observed on the patients treated by the traditional method; and an amelioration of the clinical symptoms in the temperature of the extremity and in the restoration of trophic ulcerations were observed in all cases on the patients treated with the composition of Example 1. Thus, the distance of claudication was increased from 100 meters or 200 meters to an infinite value, i.e. the patient became free from complaints, the frequent nocturnal sura spasms were abolished and the demarcation and drying of pyelous ulcers, crust formation, detachment of the crusts and the epithelium formation were observed even on aged patients.

15 In the course of the acute action of the composition of Example 1, the skin temperature was decreased by 3 to 4 °C, then it warmed back gradually and reached the original value as measurable on healthy individuals within 50 to 60 minutes. It was observed on using the composition of
20 Example 1 for the treatment of vascular stenoses that the temperature of the sick side was lower than that of the healthy one. The above temperature decrease was observed also here, but it is considered to be very significant that the temperature of the sick extremity did not increase only
25 to the starting value, but to a temperature identical with that of the healthy side, i.e. to a temperature higher than the starting value. When the agent was chronically applied, the resting skin temperature of the sick extremity was increased by 2 °C on using infrictions daily 5 times
30 for 2 weeks. An oscillometric examination was made on the patients to decide if the agent had any effect on the vascular stenosis or the tissue metabolism were improved with the retention of an unchanged vascular lumen. The oscillometric value was increased on the most part of the
35 patients /over the ankle, below and over the knee/; however

the conclusion was made that the status of the blood vessel was actually not influenced by the agent and the excellent action was achieved by an improvement in the economy of metabolism, while the blood circulation remained unchanged.

5

Test Example 2

The composition prepared according to Example 1 was used on 17 patients within the course of rehabilitation following a plaster-bandage used 6 weeks after knee
10 operations /cartilage and syndesmoplasty/. Here, a compress was used as described above. It was stated that the severe pain appearing at the initial movements was significantly or nearly completely alleviated and the enhanced muscular
15 tonus was also abolished. Thus, the restoration of the passive motion limits of the articulation was enhanced within a very short period and the tiredness, known as muscular strain, did not appear in the extremity during the active curative gymnastics. As a consequence, the rehabilitation period was shortened by 20 to 50 % and the
20 troubles connected with the movements of the patients were significantly reduced.

These effects were not observed on 10 control patients.

25

Test Example 3

The action of the composition prepared as described in Example 1 was studied on 14 patients /as compared to 8 control patients/ on such types of neuritic diseases, where the irritation of a nerve was caused by a change of
30 the condition of the musculature /functional neuritis/. In these cases, a trophic trouble was observed on the supplied area and a local blood circulation trouble was also found. The extent of the condition change was judged from the temperature of the sick area: the cooler was this
35 area, the more pronounced was considered the change. The

agent was applied to the affected area daily 5 times by
infriction for 2 weeks. After ending the treatment, the
collateral difference of 3 to 4 °C disappeared.

5 Test Example 4

 In addition to the general action of the composition
prepared as described in Example 1, it was observed that
the respiratory mid-position was shifted to a lower level
on all treated patients, i.e. the inspiratory reserve
10 volumen was increased, while the expiratory reserve volumen
was decreased. Thus, it has been proved that the composition
exerted a very advantageous effect on the economy of the
respiratory system. The maximum ventillation volumen was
increased, a fact showing that the capacity of the respiratory
15 system was also enhanced in addition to the economizing
effect.

 In the course of our investigations the following
devices have been used:

1. Skin thermometer /Servintern Rolitron licence
20 "Thermini 130"/;
2. Thermovision equipment /AGA thermovision 780 type/.

What we claim is:

1. A process for the preparation of a pharmaceutical composition influencing the tissue metabolism and having
5 a regenerating action, which c o m p r i s e s adding crystal water-free potassium aluminium sulphate to a milk kept at a temperature above 90 °C, then separating the solid material from the solution after the segregation of the obtained dispersion and optionally adding an aromatizing,
10 preserving or colouring agent to the solution.
2. A process as claimed in claim 1, which
c o m p r i s e s using 1.6 to 2.1 g of crystal water-free potassium aluminium sulphate, calculated for one litre of milk.
- 15 3. A process as claimed in claim 1 or claim 2, which c o m p r i s e s using alum heated at 300 to 400 °C as crystal water-free potassium aluminium sulphate.
4. A process as claimed in claim 1 or claim 2, which c o m p r i s e s using fatty cow milk as milk.
- 20 5. A process as claimed in any one of the claims 1 to 4, which c o m p r i s e s using a medicinal plant extract as aromatizing agent.
6. A process as claimed in claim 5, which
c o m p r i s e s using an aqueous extract of woundwort
25 /Solidago gigantea Ait. or Solidago serotina/, Glechoma hederacea L. and herb-ovy /Teucrium chamaedrys L./ as a medicinal plant extract.
7. A process as claimed in claim 5, which
c o m p r i s e s using an aqueous extract of woundwort,
30 Glechoma hederacea L., herb-ovy and silver-weed /Potentilla anserina L./ as a medicinal plant extract.
8. A process as claimed in any one of the claims 1 to 7, which c o m p r i s e s using ethanol as a preservative.
- 35 9. Pharmaceutical compositions whenever prepared by the process according to any of claims 1-8.

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 85/00042

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁴ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁴ : A 61 K 35/20, A 61 K 37/02, C 07 K 3/24, C 07 K 15/00 //A 61 K 7/48																				
II. FIELDS SEARCHED <div style="text-align: right; font-size: small;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 30%; border-bottom: 1px solid black; font-size: small;">Classification System</th> <th style="border-bottom: 1px solid black; font-size: small;">Classification Symbols</th> </tr> <tr> <td style="padding: 5px;">Int.Cl. ⁴:</td> <td style="padding: 5px;">A 61K 35/20, 35/12, 37/02, 33/06, 33/14; C 07 K 15/00, C 07K 15/24, 3/02, 3/24; A. 61 K 7/48.</td> </tr> </table> <div style="text-align: center; font-size: x-small; margin-top: 5px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁶</div>			Classification System	Classification Symbols	Int.Cl. ⁴ :	A 61K 35/20, 35/12, 37/02, 33/06, 33/14; C 07 K 15/00, C 07K 15/24, 3/02, 3/24; A. 61 K 7/48.														
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III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 5%; border-bottom: 1px solid black; font-size: x-small;">Category ⁸</th> <th style="border-bottom: 1px solid black; font-size: x-small;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="border-bottom: 1px solid black; font-size: x-small;">Relevant to Claim No. ¹³</th> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">AT, B, 41 810 (CASEIN AND MILK INDUSTRIES LIMITED), 11 April 1910 (11.04.10), see claim; page 1, lines 11-34.</td> <td style="text-align: center; vertical-align: top; padding: 5px;">(1)</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">GB, A, 6 247/A.D. 1908 (CARL ALBRECHT BAECHLER), 24 September 1908 (24.09.08), see claim 1; page 1, lines 21-43; page 2, lines 1-6, 14-29.</td> <td style="text-align: center; vertical-align: top; padding: 5px;">(1)</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">US, A, 2 721 861 (LAURENE O. PATERSON), 25 October 1955 (25.10.55), see claims 1-5; column 3, lines 8-14; column 5, lines 7-14, 23-27.</td> <td style="text-align: center; vertical-align: top; padding: 5px;">(1)</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">DE, A1, 3 001 300 (SOCIETE DES PRODUITS NESTLE S.A.), 24 July 1980 (24.07.80), see claims 1-4; page 3, lines 4-11; page 6, lines 8-16.</td> <td style="text-align: center; vertical-align: top; padding: 5px;">(1)</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">A</td> <td style="padding: 5px;">DE, C, 959 219 (MERZ & CO.), 28 February 1957 (28.02.57), see claims 1-4; page 1, lines 1-6; page 2, lines 30-44.</td> <td style="text-align: center; vertical-align: top; padding: 5px;">(1)</td> </tr> </table>			Category ⁸	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	A	AT, B, 41 810 (CASEIN AND MILK INDUSTRIES LIMITED), 11 April 1910 (11.04.10), see claim; page 1, lines 11-34.	(1)	A	GB, A, 6 247/A.D. 1908 (CARL ALBRECHT BAECHLER), 24 September 1908 (24.09.08), see claim 1; page 1, lines 21-43; page 2, lines 1-6, 14-29.	(1)	A	US, A, 2 721 861 (LAURENE O. PATERSON), 25 October 1955 (25.10.55), see claims 1-5; column 3, lines 8-14; column 5, lines 7-14, 23-27.	(1)	A	DE, A1, 3 001 300 (SOCIETE DES PRODUITS NESTLE S.A.), 24 July 1980 (24.07.80), see claims 1-4; page 3, lines 4-11; page 6, lines 8-16.	(1)	A	DE, C, 959 219 (MERZ & CO.), 28 February 1957 (28.02.57), see claims 1-4; page 1, lines 1-6; page 2, lines 30-44.	(1)
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<div style="display: flex; justify-content: space-between; font-size: x-small;"> <div style="width: 45%;"> <p>[*] Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>																				
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-bottom: 1px solid black; font-size: x-small;">Date of the Actual Completion of the International Search</td> <td style="width: 50%; border-bottom: 1px solid black; font-size: x-small;">Date of Mailing of this International Search Report</td> </tr> <tr> <td style="text-align: center; padding: 5px;">14 October 1985 (14.10.85)</td> <td style="text-align: center; padding: 5px;">17 October 1985 (17.10.85)</td> </tr> <tr> <td style="border-bottom: 1px solid black; font-size: x-small;">International Searching Authority</td> <td style="border-bottom: 1px solid black; font-size: x-small;">Signature of Authorized Officer</td> </tr> <tr> <td style="text-align: center; padding: 5px;">AUSTRIAN PATENT OFFICE</td> <td style="text-align: center; padding: 5px;"> </td> </tr> </table>			Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	14 October 1985 (14.10.85)	17 October 1985 (17.10.85)	International Searching Authority	Signature of Authorized Officer	AUSTRIAN PATENT OFFICE											
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	DE, A1, 3 029 263 (DORIS COSMETIK WERK MARTIN EBERLE & CO), 19 March 1981 (19.03.81), see claims 1-4; page 2, lines 18-22.	(1)
A	GB, A, 2 052 979 (PIERRE-JEAN ASSIER DE POMPIGNAN, SERGE LIOTET), 4 February 1981 (04.02.81), see abstract; claims 1,2; page 1, lines 1-55.	(1)
A	EP, A1, 0 009 464 (VERBAND AARGAVISCHER KÄSEREI- UND MILCHGENOSSENSCHAFTEN), 2 April 1980 (02.04.80), see abstract; claims 1-3.	(1)

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